

AMENDMENTS TO THE CLAIMS

The following amended claim listing replaces all prior versions of the claims in the application.

1-19. (Canceled)

20. (Previously presented) A method of preemptively inhibiting pain and inflammation at a wound during a surgical procedure, comprising delivering to a wound during a surgical procedure a solution comprising at least one tumor necrosis factor (TNF) soluble receptor, wherein the solution is applied locally and perioperatively to the surgical site.

21. (Canceled)

22. (Previously presented) The method of Claim 20, wherein the soluble receptor is selected from the groups of soluble receptors consisting of sTNFR and chimeric rhTNFR:Fc.

23. (Canceled)

24. (Canceled)

25. (Currently amended) The method of Claim 20, wherein the solution further comprises at least one additional pain/inflammation inhibitory agent selected to act on a different molecular target than the target upon which the soluble receptor acts.

26. (Previously presented) The method of Claim 20, comprising continuously applying the solution to the wound.

27. (Previously presented) The method of Claim 26, comprising continuously irrigating the wound with the solution.

28. (Previously presented) The method of Claim 20, wherein the solution is applied by irrigation of the wound.

29. (Previously presented) The method of Claim 20, wherein the solution is locally applied to the wound in the absence of metabolic transformation.

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30. (Previously presented) The method of Claim 20, wherein the perioperative application of the solution comprises intraprocedural application together with preprocedural or postprocedural application of the solution.

31. (Previously presented) The method of Claim 30, wherein the perioperative application of the solution comprises preprocedural, intraprocedural and postprocedural application of the solution.

32. (Previously presented) The method of Claim 30, wherein the solution is continuously applied to the wound.

33. (Previously presented) The method of Claim 20, wherein the soluble receptor in the solution is delivered locally at a concentration of no greater than 1,000 nanomolar.

34. (Previously presented) The method of Claim 20, wherein the soluble receptor in the solution is included at a concentration or dosage that is sufficient to provide a level of inhibitory effect at the wound when delivered locally to the wound and that results in a plasma concentration that is less than a plasma concentration that would be required to achieve the same level of inhibitory effect at the wound when delivered systemically.

35. (Previously presented) The method of Claim 25, wherein each of the additional agents in the solution is delivered locally at a concentration of no greater than 100,000 nanomolar.

36. (Previously presented) The method of Claim 25, wherein each of the plurality of agents in the solution applied is included at a concentration or dosage that is sufficient to provide a level of inhibitory effect at the wound when delivered locally to the wound and that results in a plasma concentration that is less than a plasma concentration that would be required to achieve the same level of inhibitory effect at the wound when delivered systemically.

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37. (Previously presented) The method of Claim 25, wherein the at least one pain/inflammation inhibitory agent is selected from the group consisting of: serotonin receptor antagonists; serotonin receptor agonists; histamine receptor antagonists; bradykinin receptor antagonists; kallikrein inhibitors; tachykinin receptor antagonists including neurokinin<sub>1</sub> receptor subtype antagonists and neurokinin<sub>2</sub> receptor subtype antagonists; calcitonin gene-related peptide receptor antagonists; interleukin receptor antagonists; phospholipase inhibitors including PLA<sub>2</sub> isoform inhibitors and PLC<sub>γ</sub> isoform inhibitors; cyclooxygenase inhibitors; lipooxygenase inhibitors; prostanoid receptor antagonists including eicosanoid EP-1 receptor subtype antagonists and eicosanoid EP-4 receptor subtype antagonists and thromboxane receptor subtype antagonists; leukotriene receptor antagonists including leukotriene B<sub>4</sub> receptor subtype antagonists and leukotriene D<sub>4</sub> receptor subtype antagonists; opioid receptor agonists including μ-opioid receptor subtype agonists, δ-opioid receptor subtype agonists, and κ-opioid receptor subtype agonists; purinoceptor agonists and antagonists including P<sub>2Y</sub> receptor agonists and P<sub>2X</sub> receptor antagonists; and ATP-sensitive potassium channel openers.

38. (Previously presented) The method of Claim 37, wherein the selected pain/inflammation inhibitory agents are delivered locally at a concentration of: 0.1 to 1000 nanomolar for soluble receptors; 0.1 to 10,000 nanomolar for serotonin receptor antagonists; 0.1 to 2,000 nanomolar for serotonin receptor agonists; 0.01 to 1,000 nanomolar for histamine receptor antagonists; 0.1 to 10,000 nanomolar for bradykinin receptor antagonists; 0.1 to 1,000 nanomolar for kallikrein inhibitors; 0.1 to 10,000 nanomolar for neurokinin<sub>1</sub> receptor subtype antagonists; 1.0 to 10,000 nanomolar for neurokinin<sub>2</sub> receptor subtype antagonists; 1 to 1,000 nanomolar for calcitonin gene-related peptide receptor antagonists; 1 to 1,000 nanomolar for interleukin receptor antagonists; 100 to 100,000 nanomolar for PLA<sub>2</sub> isoform inhibitors; 100 to 200,000 nanomolar for cyclooxygenase inhibitors; 100 to 10,000 nanomolar for lipooxygenase

inhibitors; 100 to 10,000 nanomolar for eicosanoid EP-1 receptor subtype antagonists; 100 to 10,000 nanomolar for leukotriene B<sub>4</sub> receptor subtype antagonists; 0.1 to 500 nanomolar for  $\mu$ -opioid receptor subtype agonists; 0.1 to 500 nanomolar for  $\delta$ -opioid receptor subtype agonists; 0.1 to 500 nanomolar for  $\kappa$ -opioid receptor subtype agonists; 100 to 100,000 nanomolar for purinoceptor antagonists; and 0.1 to 10,000 nanomolar for ATP-sensitive potassium channel openers.

39. (Currently amended) A solution for use in the preemptive inhibition of pain and inflammation at a wound during a surgical procedure, comprising at least one tumor necrosis factor (TNF) soluble receptor in a liquid irrigation carrier, the soluble receptor being included at a concentration ~~or in a dosage form~~ that is sufficient to provide a level of inhibitory effect at the wound when delivered locally to the wound and that results in a plasma concentration that is less than a plasma concentration that would be required to achieve the same level of inhibitory effect at the wound when delivered systemically.

40. (Canceled)

41. (Previously presented) The solution of Claim 39, wherein the soluble receptor is selected from the groups of soluble receptors consisting of sTNFR and chimeric rhTNFR:Fc.

42. (Canceled)

43. (Canceled)

44. (Previously presented) The solution of Claim 39, which further comprises at least one additional pain/inflammation inhibitory agent selected to act on a different molecular target than the soluble receptor.

45. (Previously presented) The solution of Claim 44, wherein the soluble receptor in the solution is included at a concentration of no greater than 1,000 nanomolar and each of the additional agents in the solution is included at a concentration of no greater than 100,000

nanomolar, adjusted for dilution in the absence of metabolic transformation, at an intended local delivery site.

46. (Previously presented) The solution of Claim 44, wherein each of the plurality of agents in the solution is included at a concentration or dosage form that is sufficient to provide a level of inhibitory effect at the wound when delivered locally to the wound and that results in a plasma concentration that is less than a plasma concentration that would be required to achieve the same level of inhibitory effect at the wound when delivered systemically.

47. (Previously presented) The solution of Claim 44, wherein the at least one additional pain/inflammation inhibitory agents are selected from the group consisting of: serotonin receptor antagonists; serotonin receptor agonists; histamine receptor antagonists; bradykinin receptor antagonists; kallikrein inhibitors; tachykinin receptor antagonists including neurokinin<sub>1</sub> receptor subtype antagonists and neurokinin<sub>2</sub> receptor subtype antagonists; calcitonin gene-related peptide receptor antagonists; interleukin receptor antagonists; phospholipase inhibitors including PLA<sub>2</sub> isoform inhibitors and PLC<sub>γ</sub> isoform inhibitors; cyclooxygenase inhibitors; lipoxygenase inhibitors; prostanoid receptor antagonists including eicosanoid EP-1 receptor subtype antagonists and eicosanoid EP-4 receptor subtype antagonists and thromboxane receptor subtype antagonists; leukotriene receptor antagonists including leukotriene B<sub>4</sub> receptor subtype antagonists and leukotriene D<sub>4</sub> receptor subtype antagonists; opioid receptor agonists including μ-opioid receptor subtype agonists, δ-opioid receptor subtype agonists, and κ-opioid receptor subtype agonists; purinoceptor agonists and antagonists including P<sub>2Y</sub> receptor agonists and P<sub>2X</sub> receptor antagonists; and ATP-sensitive potassium channel openers.

48. (Previously presented) The solution of Claim 47, wherein the additional pain/inflammation inhibitory agents are included at a concentration of: 0.1 to 10,000 nanomolar for serotonin receptor antagonists; 0.1 to 2,000 nanomolar for serotonin receptor agonists; 0.01 to

1,000 nanomolar for histamine receptor antagonists; 0.1 to 10,000 nanomolar for bradykinin receptor antagonists; 0.1 to 1,000 nanomolar for kallikrein inhibitors; 0.1 to 10,000 nanomolar for neurokinin<sub>1</sub> receptor subtype antagonists; 1.0 to 10,000 nanomolar for neurokinin<sub>2</sub> receptor subtype antagonists; 1 to 1,000 nanomolar for calcitonin gene-related peptide receptor antagonists; 1 to 1,000 nanomolar for interleukin receptor antagonists; 100 to 100,000 nanomolar for PLA<sub>2</sub> isoform inhibitors; 100 to 200,000 nanomolar for cyclooxygenase inhibitors; 100 to 10,000 nanomolar for lipooxygenase inhibitors; 100 to 10,000 nanomolar for eicosanoid EP-1 receptor subtype antagonists; 100 to 10,000 nanomolar for leukotriene B<sub>4</sub> receptor subtype antagonists; 0.1 to 500 nanomolar for  $\mu$ -opioid receptor subtype agonists; 0.1 to 500 nanomolar for  $\delta$ -opioid receptor subtype agonists; 0.1 to 500 nanomolar for  $\kappa$ -opioid receptor subtype agonists; 100 to 100,000 nanomolar for purinoceptor antagonists; and 0.1 to 10,000 nanomolar for ATP-sensitive potassium channel openers.

49. (Currently amended) A solution for use in the preemptive inhibition of pain and inflammation at a wound during a surgical procedure, comprising at least one tumor necrosis factor (TNF) soluble receptor in a liquid carrier for perioperative application, the soluble receptor being included at a concentration ~~or in a dosage form~~ that is sufficient to provide a level of inhibitory effect at the wound when delivered locally to the wound and that results in a plasma concentration that is less than a plasma concentration that would be required to achieve the same level of inhibitory effect at the wound when delivered systemically.

50. (Currently amended) A solution for use in the preemptive inhibition of pain and inflammation at a wound during a surgical procedure, comprising at least one tumor necrosis factor (TNF) soluble receptor and at least one additional agent that is an inhibitor of pain and/or inflammation in a liquid carrier, the soluble receptor and the at least one additional agent being selected to act on differing molecular targets and included at a concentration ~~or in a dosage form~~

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that is sufficient to provide a level of inhibitory effect at the wound when delivered locally to the wound and that results in a plasma concentration that is less than a plasma concentration that would be required to achieve the same level of inhibitory effect at the wound when delivered systemically.

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